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TREM-1 and its potential ligands in non-infectious diseases: from biology to clinical perspectives

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ABSTRACT

Triggering receptor expressed on myeloid cells-1 (TREM-1) is expressed on the majority of innate immune cells and to a lesser extent on parenchymal cells. Upon activation, TREM-1 can directly amplify an inflammatory response. Although it was initially demonstrated that TREM-1 was predominantly associated with infectious diseases, recent evidences shed new light into its role in sterile inflammatory diseases. Indeed, TREM-1 receptor and its signaling pathways contribute to the pathology of several non-infectious acute and chronic inflammatory diseases, including atherosclerosis, ischemia reperfusion-induced tissue injury, colitis, fibrosis and cancer. This review, aims to give an extensive overview of TREM-1 in non-infectious diseases, with the focus on the therapeutic potential of TREM-1 intervention strategies herein. In addition, we provide the reader with a functional enrichment analysis of TREM-1 signaling pathway and potential TREM-1 ligands in these diseases, obtained via *in silico* approach. We discuss pre-clinical studies which show that TREM-1 inhibition, via synthetic soluble TREM-1 protein mimickers, is effective in treating (preventing) specific inflammatory disorders, without significant effects on antibacterial response. Further research aimed at identifying specific TREM-1 ligands, in different inflammatory disorders, is required to further unravel the role of this receptor, and explore new avenues to modulate its function.

Contents

Abbreviations: AGA, acute gouty arthritis; AP-1, activator protein-1; BAL, bronchial alveolar lavage; BD, intestinal Behcet's disease; BPAR, biopsy proven acute rejection; CAD, coronary artery disease; CARD, caspase recruitment domain-containing protein; CAT, colitis-associated tumorigenesis; CD, Crohn's disease; CIA, collagen-induced arthritis; DAMPs, damage associated molecular patterns; DGF, delayed graft function; ERK, extracellular signal-regulated; HMGB1, high mobility group box-1; HSP, heat shock proteins; IBD, inflammatory bowel disease; IFTA, interstitial fibrosis/tubular atrophy; IR, ischemia-reperfusion; IRAK, IL-1R-associated kinases; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; Myd88, myeloid differentiation primary response; Nf-κB, nuclear factor-κB; NLR, Nod-like receptor; NOD, nucleotide-binding oligomerization domain; NSCLC, non-small cell lung cancer; PAMPs, pathogen-associated molecular patterns; PBC, peripheral blood cells; PGN, peptidoglycan; PI3K, phosphatidylinositol 3-kinase; PRR, pattern recognition receptors; RA, rheumatoid arthritis; RIP2, receptor-interacting serine/threonine-protein 2; SNV, single nucleotide variants; sTREM-1, soluble TREM-1; TLR, Toll like receptor; TREM-1, triggering receptor expressed on myeloid cells-1; UC, ulcerative colitis; UO, ureteral obstruction.

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1. Introduction

Innate immune cells are key players in the recognition of invading pathogens or alarming the host during tissue damage. The magnitude of inflammation relies on the activation of pattern recognition receptors (PRR). One family of PRRs is the family of Toll-like receptors (TLRs), which are well known for their role in innate immunity during infectious and non-infectious diseases. More recently, another family of innate immune receptors was described to interact with TLRs and influence the extent of the inflammatory response: the triggering receptors expressed on myeloid cells (TREMs) (Arts, Joosten, van der Meer, & Netea, 2012; Klesney-Tait, Turnbull, & Colonna, 2006). The TREM-family comprises both activating and inhibitory receptors. Among these family members, TREM-1 represent the most studied activating receptor, whereas TREM-2 is widely known as an inhibitor of the inflammatory response. Activation of TREM-1 is known to trigger and amplify inflammation, especially through synergism with TLR signaling. Early after the discovery of TREM-1, it was believed that TREM-1 was merely involved in non-infectious diseases, and research was mainly focused on TREM-pathogen interaction as described in several elegant reviews (Gibot, 2005, 2006; Roe, Gibot, & Verma, 2014; Sharif & Knapp, 2008). However, more recent research shows that TREM-1 is also involved in non-infectious diseases and this review aims to give an overview of the expression, and function of TREM-1 receptor and its ligands herein. Moreover, intervention studies that examined TREM-1 receptor modulation in non-infectious diseases, were included. Lastly, because several research questions regarding the TREM-1 ligand and pathway synergism, are still unanswered, we performed an *in silico* analysis of putative TREM1-ligand expression and pathway enrichment in several sterile inflammatory diseases.

2. TREM-1 signaling pathway

2.1. TREM-1 pathway

First experiments performed by Colonna and colleagues showed that TREM-1 is mainly expressed on myeloid cells such as monocytes/macrophages and granulocytes. However, ongoing research shows that during inflammation, TREM-1 is also detected on parenchymal cell types such as bronchial, corneal, gastric epithelial cells, and hepatic endothelial cells (Barrow et al., 2004; Chen, Laskin, Gordon, & Laskin, 2008; Rigo et al., 2012; Schmausser et al., 2008). TREM-1 is present in 2 forms: as a membrane-bound receptor and as soluble protein (Figs. 1 and 2). Membrane TREM-1 features 3 distinct domains: an Ig-like structure (most likely responsible for ligand binding), a transmembrane part and a cytoplasmic tail which associates with the adaptor molecule TYROBP (TYRO protein tyrosine kinase-binding protein, more frequently called DAP12: DNAX activating protein of 12 kDa) (Colonna, 2003). This complex is stabilized through a unique electrostatic interaction between a negatively charged (−) aspartic acid in DAP12, and a positively charged (+) lysine in TREM-1 intracytoplasmic tail, which is necessary for signal transduction. Following TREM-1 engagement, the cytoplasmic part of DAP12 containing ITAMs (Immunoreceptor tyrosine-based activation motif) becomes phosphorylated at its tyrosine residue, providing a docking site for protein tyrosine kinases: ZAP70 (Zeta-chain-associated protein kinase 70) and SYK (Spleen Tyrosine Kinase). SYK promotes the recruitment and tyrosine phosphorylation of adaptor complexes that contain Cbl (Casitas B-lineage Lymphoma), SOS (Son of sevenless) and GRB2 (Growth Factor Receptor Binding Protein-2), which results in downstream signal transduction through PI3K, PLC-Gamma (Phospholipase-C-Gamma) and the ERK pathways. These pathways induce Ca^{2+} mobilization, rearrangement of the actin cytoskeleton and activation of transcription factors such as Elk1 (ETS domain-containing protein), NFAT (Nuclear Factor of Activated T-Cells), AP1, c-Fos, c-Jun and Nf-κB, which transcribe genes that encode pro-inflammatory cytokines, chemokines and cell-surface molecules. In addition, TREM1-induced PI3K and ERK pathway activation can promote mitochondrial integrity and cell survival by inactivating pro-apoptotic factors: BID (BH3-Interacting Domain Death agonist), BAD (BCL-2-Antagonist of cell Death) and BAX (BCL-2-Associated X-Protein) and inhibiting CytoC (Cytochrome-C) release from mitochondria (Yuanet al., 2014, 2016).

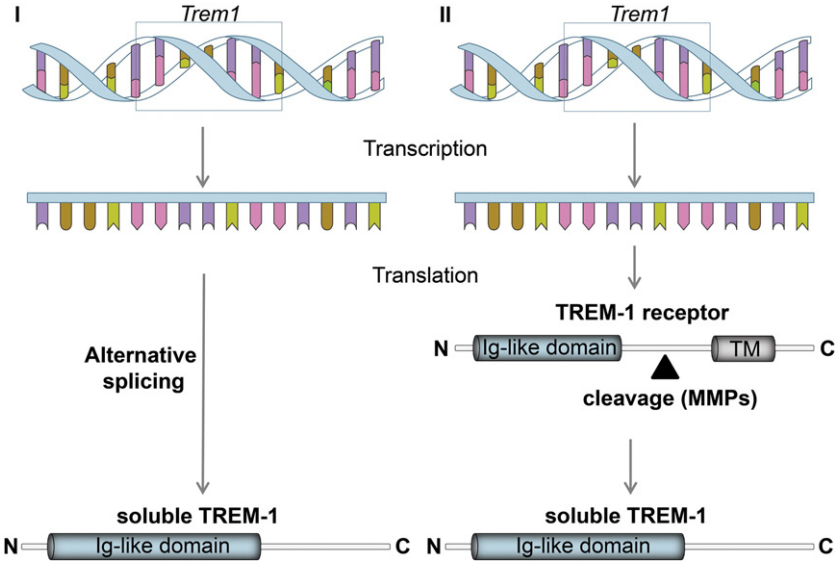

Fig. 1. TREM-1 receptor and soluble protein regulation. Graphical representation of the two hypotheses of soluble TREM-1 protein (sTREM-1) origins. Upon transcription, alternative splicing of the *Trem1* gene can result in the synthesis of a smaller protein, which contains only the immuoglobulin-like domain (Ig-like domain). This protein is referred to as sTREM-1 (I: left). The canonical translation process produces the TREM-1 receptor protein, which consists of the Ig-like domain and a transmembrane domain (TM). This receptor, upon proteolytic cleavage by metalloproteinases (MMPs), results in sTREM-1 protein generation (II: right).